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Review

Past, present and future of Covid-19 pandemic; review of the pathophysiology and clinical management

Mirza Zeeshan Sikandar[1], Aiman Fatima[1], Syed Imran Ali Shah[2]
[1]Department of Biochemistry, Central Park Medical College, Lahore, Pakistan
[2]Department of Biochemistry, University of Hafr AlBatin, Saudi Arabia

Abstract

The coronavirus disease (COVID-19) pandemic has been caused by the worldwide infectious spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Its mechanism of action involves RNA virus implantation into the cell's cytoplasm and the hijack of transcriptional machinery. The infection primarily afflicts the pulmonary system, resulting in multiple complications including, but not limited to, ground glass opacities seen on imaging. Characteristic features of COVID-19 involve pneumonia, shortness of breath, asthma, nasal congestion, sore throat, fever, fatigue, myalgia and it also encompasses a wide variety of other systemic symptoms. Multiple pharmaceutical agents have been tried as a treatment for COVID-19 but the results are inconsistent. With the intention of stopping person- to- person transmission, health measures such as quarantine and social distancing have been adopted, but the implementation was difficult. After the first wave of the pandemic, the second wave surfaced with a clear resurgence of cases followed by a third wave. The present review summarizes what is known about COVID-19 and explores the factors behind the resurgence.

Keywords

COVID-19; RNA Virus; Quarantine; Myalgia; Fever; Fatigue; Anti-inflammatory drugs; Resurgence

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Corresponding Author: Mirza Zeeshan Sikandar, Department of Biochemistry, Central Park Medical College, 31-km Ferozepur Road (near Kahna Nau), 54600, Lahore, Pakistan.
E-mail: m.zee.shan@hotmail.com P: 0336-8656736
Corresponding Author ORCID ID: https://orcid.org/0000- 0002-5499-7884

Introduction

The novel coronavirus disease (COVID-19) emerged as a public health emergency in China, and in a short span of only a few months, it engulfed the entire world that could not help but suffer the devastating effects of this potentially fatal disease [1]. COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has adapted the features of a pandemic as identified by World Health Organization (WHO) [2-4].

SARS-CoV-2 is a beta coronavirus, similar in genome to the bat virus that is considered to be the natural host [5]. In December 2019, since its beginning in Wuhan, China, it spread worldwide [6]. Historically, coronaviruses have a total of 7 types, two of which are known to be the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), presented in China in 2002, and its animal- to- human transmission was traced to civets. The second severe coronavirus variant transmitted from dromedary camels, was observed in Saudi Arabia in 2012 and termed the Middle-Eastern respiratory syndrome virus (MERS-CoV) [7]. The current outbreak of SARS-CoV-2 originated in a wholesale seafood market of Wuhan city, in the Chinese province of Hubei. The outbreak was aggravated by high human- to- human transmission [8]. Coronavirus encompasses 2 major modes of transmission, including human-to-human transmission (HHT) and animal-to-human (zoonotic transmission) [9].

The virus and its nature

The virus causing COVID-19 has been labeled as SARS-CoV-2 due to its remarkable homology with SARS-CoV, which presented with Acute Respiratory Distress Syndrome (ARDS) and high mortality rates in 2002-2003 [10]. Interestingly, there is a clear similarity between the clinical presentation of COVID-19 and the disease caused by other respiratory viruses. This similarity with SARS-CoV is less than seventy percent, along with a high mutational ability of the SARS-CoV-2, which posed obstacles to the development of an effective vaccine [11]. The main proteins present in and on the surface of the virus include Membrane protein (M), Envelope protein (E), Nucleocapsid protein (N) and Spike protein (S). Mechanisms involving immune targeting of these viral protein epitopes by B and T cells have been employed to develop vaccines, which have been put through clinical trials worldwide [12]. Any stoppage in the transmission chain of COVID-19 through effective vaccinations, social measures and/or treatment on a larger scale can help inhibit its spread [13].

Mechanism and Infectivity:

COVID-19 is highly infective as the SARS-CoV-2 consists of untranslated RNA regions in the form of 5'UTR, replicase complex, S gene, M gene, E gene, N gene and several other untranslated regions that make it more virulent [14]. SARS-CoV-2 affects helper T cells and results in progressive, severe and systemic inflammation that may even lead to fulminant myocarditis or even disseminated intravascular coagulation (DIC). Inflammatory markers involved in this inflammatory cascade include interleukins like IL-6, inflammatory cytokines, membrane lipopolysaccharides, D-dimers, fibrinogen, angiotensin II release through the renin-angiotensin-aldosterone-system (RAAS), reactive oxygen species (ROS) and pro-inflammatory products released from natural killer (NK) cells (Figure 1) [15].

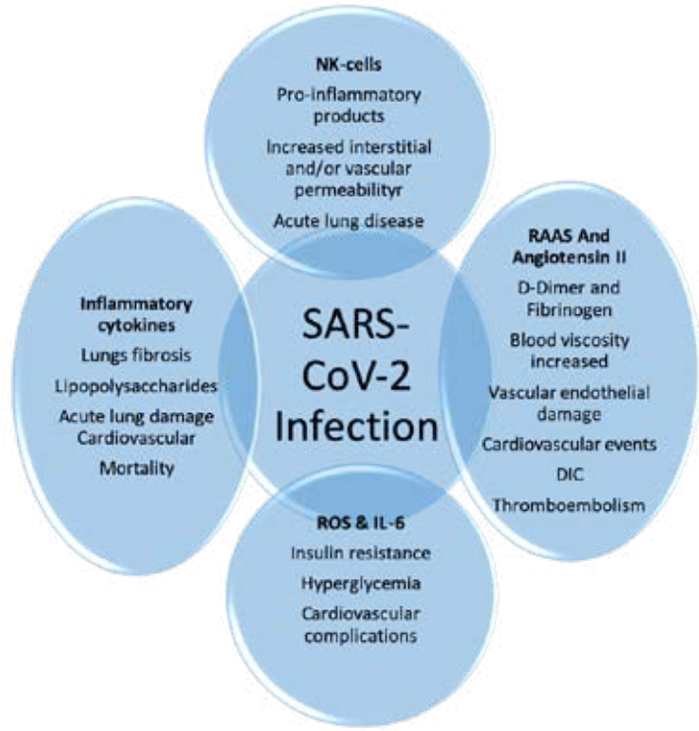

Figure 1. Mechanism of Inflammation-induced complications of COVID-19

SARS-CoV-2 is a positively charged and single-stranded RNA virus, which infects by planting itself into the cell's cytoplasm. The hijacking of the transcriptional machinery involves an intricate initial mechanism involving the angiotensin-converting enzyme 2 (ACE-2), which allows receptors. SARS-CoV-2 interaction with the ACE-2 receptors and transmembrane serine protease 2 to gain entry into the epithelial cells of the lungs, as well as other organs such as the brain, kidneys, lungs, heart, pharynx and liver [16]. ACE-2 and RAAS counter-act each other and downregulation of one system in COVID-19 infection may trigger high immunological response leading to grave complications and organ failure [17].

Global Approaches for Pandemic Management:

Different models and approaches have been used to manage the pandemic around the world in different countries and regions. Important components involve reliable surveillance, news reports, providing detailed patient level data and construction of outbreak management. Surveillance is important as it can unmask and trace down undocumented cases, which have the highest risk of spread. Fatigued and overwhelmed healthcare systems have required encouragement and support of all kinds, which at times have not been forthcoming. [18].

Upper respiratory swab/sputum/aspirates/nasopharyngeal content tested for SARS-CoV-2 Real-time polymerase chain reaction (RT-PCR) test can allow the establishment of effective identification of COVID-19 positive patients and their timely isolation, which can reduce further transmission.

A linear correlation has been observed between the risk of contracting COVID-19 and exposure with a COVID-19 positive patient. Distance and duration of exposure also determined the transmissibility; greater the duration of exposure greater would be transmission and vice versa

The Italian catastrophe was the first major concern arising

Figure 2. Comparison of cases and mortality (per million) between Pakistan and other countries

after the Chinese outbreak of COVID-19. It is widely perceived that the susceptibility of the Italian population to morbidity and mortality from COVID-19 was predominantly due to the large proportion of elderly individuals [19]. It has also been claimed that an earlier mass-scale influenza vaccination drive led to a hyperactive immune response, leading to elevated death rates (available at: https://emedicine.medscape.com/article/2500139-overview).

In some other parts of Europe, subjecting the susceptible population to safer lockdown arrangements suppressed their chances of getting the virus and reduced deaths. However, this approach eliminated the exposed healthy population, leading to even greater number of victims. Lockdown in developed countries has been shown to be 90 percent effective due to effective implementation, population education and awareness, but the same cannot be said about the developing world [21]

After massive endemic in USA, The Tracker of the New York Times Vaccine has listed a number of vaccines for continued clinical trials, as well as approval for full use. A process of investigating number of immunotherapies and treatment combinations is still going on in the United States of America. Following ongoing government struggle in tackling the great percentage of active cases and induced resultant deaths, two mRNA vaccines, including Pfizer and Moderna, have received FDA approval by December 2020. However, vaccines like Johnson and Johnson are nearing their final trials or phase 3 trials and can portray good prospects.

Experience from Pakistan: Pakistan, as a developing country, lacked population awareness and resources for a complete lockdown. Poor socio-economic conditions and the overburdened state systems did not permit the government to provide for a large population that would have undergone unemployment as a result of lockdown. In order to avoid such chaos, only a regional and partial lockdown was observed in Pakistan [22].

The epidemic curve of COVID-19 has been categorized into two distinct waves with an intervening plateau phase after the first wave, followed by an exponential resurgence of cases upon the arrival of the second wave [23]. Immunological responses have been greatly emphasized for the double peak epidemic curve, and both innate and adaptive immunity play a crucial role in responses generated against viral exposure [24]. Innate immunity, if active and efficient, including natural killer cells (NK) cells, interferon, and complement systems of protein and IgA immunoglobulin secreted in body fluids, can inhibit the virus in initial phases. However, the mode of action of adaptive immunity requires the initial viral load and viral replication for presenting its viral particles to CD8+T along with MHC antigens class1 developing memory cells [25].

Clinical Features and Diagnostic Approaches

The incubation period of the SARS-CoV-2 has been averaged as 6.4 days with a range from 0 to 24 days. Symptoms typically appear 5- 7 days after initial exposure to the virus [26]. SARS_CoV-2 mainly affects the pulmonary system [27] and eventually leads to ground glass opacities and patches in the lungs [28], but every infected person does not develop symptoms [29]. A number of affected individuals developing complications were found to have chronic comorbidities [30] like hypertension, diabetes, coronary heart disease, cerebral infarction, chronic bronchitis, asthma and others [31]. Among adults across all age groups, males are more affected than females. The clinical manifestations observed in patients suffering from COVID-19 include a spectrum of different combinations and intensities of various signs and symptoms, including some major indications like fever and cough in up to 80% of cases with fever of 101oF or above. Shortness of breath has been observed in 31% of clinical cases with the coarseness of breathing sounds upon auscultation.

Table 1. Clinical signs and symptoms of COVID-19 infection

Features	Values in COVID	Reference Range	Clinical
Respiratory Rate	>30 breathes/min	12-16/min	Raised
Oxygen Saturation	< 93%	> 95%	Decreased
Temperature	> 100 F	98F – 99F	Raised
Sensations	Loss of smell and taste	Presence of sense of Smell and Taste	Absent

Physicians experience diagnostic traps in treating COVID-19 patients. One good example is the pneumonia-like appearance on the X-ray that can mask the virus and perplex the physician. In 50 percent of the cases, CT remains normal for 0 to 2 days after the onset of flu-like symptoms [32]. COVID-19 RT-PCR sensitivity is low (60-70 percent). X-ray may show peripheral or multi-focal opacities, but PCR may still be negative [33]. The virus attacks the respiratory system, resulting in severe acute respiratory syndrome characterized by pneumonia, shortness of breath, asthma, nasal congestion, sore throat, fever, fatigue and myalgia [34]. Apart from respiratory involvement, the virus has also been shown to enter and disrupt the gastrointestinal, hepatic and neurological domains [35]. The worst CT findings appear 9- 13 days after contracting SARS-CoV-2, after which CT scan begins to clear and shows a decrease in the ground glass opacities provided no further complications develop [36, 37].

As the world is progressing to the era of molecular mechanics, thus COVID-19 is ideally detected using RT-PCR [38]. As the infection persists, immunoglobulins of IgG and IgM types are produced as a response to control the infection [39]. COVID-19 RT-PCR has a low sensitivity of 60 to 70 percent and mostly

depends on the degree of shedding of the virus by the individual in the oropharynx secretions [40]. Complete blood counts giving a viral picture, including leucopenia or decreased lymphocyte count, are also suggestive of COVID-19 in patients with a history of possible exposure. Serum Ferritin, C-reactive protein and D-dimer levels also are useful in the diagnostic and prognostic management of COVID-19 as they reflect inflammatory and immunological responses to the viral invasion [41]. The SARS-Cov2 antibody test is efficient after 1 to 3 weeks following the appearance of symptoms [42].

Radiological aspects such as observance of a pneumonia pattern [43] are important in assessing disease severity, and they are assessed better and earlier on CT-scan rather than on chest X-ray [44]. In 57% of cases, these are referred to as ground- glass opacities or consolidations, or cavitation, depicting airspace disease [45].

Treatment Choices

The search for an absolute treatment of COVID-19 has been going on for the last year, but a single magical therapeutic agent has remained elusive. The combination of anti-influenza agent Oseltamivir and anti-HIV agent Lopinar/Ritonavir has been used together, but no definitive comment can be made on their efficacy [46] Chloroquine/hydroxyl-chloroquine administration in some studies were shown to interfere with the replication cycle, but larger clinical studies have not shown much therapeutic benefit [47]. Immunity boosters such as multi-vitamins and the use of vitamin D may potentially interfere with the intensity of the disease as well as quicker recovery due to their suggested role against aggravated allergic and anti-inflammatory response [48-51]. Antibiotics like azithromycin for bacterial complications has also been used. Anti-inflammatory drugs have been employed to reduce elevated inflammatory and immune responses and extend protection against cytokine strike complications and risks [52].

Nucleoside analog trials such as Remdesvir proved to be useful against a wide range of RNA viruses, but their use in COVID-19 has not yet been established [53-57]. Table 2 lists the various pharmacologic agents that have been tried in the treatment of COVID-19.

Preventive Measures

With the intention of stopping person- to -person transmission, health measures such as Isolation, Quarantine, Social distancing, and Community containment were taken into consideration [77]. The elimination of viruses from the surfaces by chemical means, especially in places with a high risk of contamination, has further reduced their spread. Furthermore, measures at an individual level that include frequent hand washing, use of sanitizer, and wearing of masks have been proven to be beneficial [78-80]. Timely dissemination of information in the media is crucial to effective administration of personal protection, limiting imports, public gatherings and anything aggravating chances of contact and spread. Proper Screening and travel restrictions can potentially withhold the spread of the virus to a great degree. Training of Medical and non-medical teams should avoid reducing the burden on health care professionals [81].

Vaccination

Collaborative initiatives between public and private sectors and facilitated by the World Health Organization (WHO) have allowed for rapid vaccine development programs, which have led to successful production and development of many different vaccines against SARS-CoV-2 involving various mechanisms of action. Pfizer-BioNTech was the first one to gain recognized approval. It has been shown to confer 95% protection against COVID-19 in people older than 16 years of age through a two-shot regimen with the second dose given two weeks after

Table 2. Impact of several drugs and their consequences in COVID-19 patients

Treatment options	Proposed Mechanism	Contraindications	Side effects/toxicities
Hydroxy-Choloroquine (HCQ)/ Choloroquine (CQ) [58,59]	Inhibition of viral protein synthesis	Any case of known hypersensitivity Retinal defects	Prolonged QT interval resulting in arrhythmia - Bone marrow and immunity suppression - Myopathy and Seizures - Retinopathy
Azithromycin [60,61]	Inhibition of bacterial protein synthesis and potential anti-viral role	Contraindicated in hypomagnesia and hypokalemia as well as myasthenia gravis	- Prolonged QT interval
Remdesivir [62,63]	Analog to adenosine; Quick termination of viral RNA		Kidney complication Interference with transaminases levels
Ritonavir/Lopinavir [64,65]	HIV-1 protease inhibitor stopping viral maturation and infection; same mode of action for SARS-CoV-2		Nausea and GIT- related complications are common. In severe cases may cause liver, pancreas and cardiac complications and inflammations
Favipiravir [66,67]	Chain termination due to inhibition in the action of RNA dependent type of RNA polymerase		Neutropenia and diarrhea
Ribavirin [68,69]	Guanosine analog and causes inhibition of RNA polymerase	Pregnant female or men with a pregnant partner or hemoglobinopathy patients	Teratogenic effects and induced cases of hemolytic anemia
Ivermectin [69,71]	Reduction of viral RNA and anti-parasitic effect		May induce rashes on the skin and related muscle and joint pain
Immunoglobulin [72,73]	Neutralization of virus due to injection of antibodies collected from Covid-19 recovered patients		Induced headache, fever, malaise, flushing, thrombo-sis, renal impairment and cardiac arrhythmias
Corticosteroids [74,75]	Anti -inflammatory role against cytokines (1L- 6, 1L-1, 1L-12, 1L-8, TNFα) and decreased pathological damage	Patients with diabetes, hypertension and other chronic ongoing infections.	Short term does not cause complications but long-term use can cause weight gain, osteoporosis, hypertension and diabetes.
Interferon [76,77]	Proteins produced by the immune system; immunity boosters		Fever, chills, flu-like symptoms, fatigue, headache and weakness
Tocilizumab [78,76]	Affinity for IL-6 receptors; recombinant monoclonal antibody (human IL-6)	Any previous allergy established to tocilizumab and patients with throm-bocytopenia and neutropenia	Respiratory tract infection including tuberculo-sis, nasopharyngitis and other complications like headache, hepatic toxicity, allergic reactions and GIT perforations.

Table 3. Vaccination and its overview

Vaccine	Mechanism of Action	Effectively and Safety
Pfizer-BioNTech	Vaccine is mRna based against S or Spike Protein	95% effective (100% effective in preventing hospitalization) Generally zero to mild symptoms observed after administration
Modema	mRNA based	95% effective (100% effective in preventing hospitalization)
AstraZenecca	Adenovirus-based	70% effective in prevention
Sinovac/Pharm	Inactivated SARS-CoV-2 virus	50.38% to 91.25%
CanSino Biologics	Viral vector; SARS-Cov2 antigen onto adenovirus	65.7% effective in prevention of symptomatic cases
Sputnik-V	Adenovirus based	91.4% effective
Novavax	Protein-based	89.3%
Johnson and Johnson	Adenovirus based	66% efficacy in prevention (In USA, this value is 70%)

the first. Safety over a median of 2 months has also been demonstrated to be similar to that of other viral vaccines (available at: https://www.biospace.com/article/comparing-covid-19-vaccines-pfizer-biontech-moderna-astrazeneca-oxford-j-and-j-russia-s-sputnik-v/)

Table 3 provides a list of some of the vaccines that are currently being used in the world and their mechanisms of action [84]. Vaccine- induced immunity is considerably different from naturally induced immunity, as the majority of the population (up to 74 percent) who are asymptomatic or have mild symptoms may develop very few antibodies and this may not last long. This seriously changes the dynamics of the possible chances of herd immunity. Keeping tracks of subjects after vaccination is a key feature of any vaccine trial. Making comprehensive data of T-cell and antibody presentation will allow a record of the vaccine- induced protection and its effects later on [83].

Conclusion:

The importance of a well-coordinated approach cannot be denied, and the management of the second wave could be a deciding point in a successfully combating the COVID-19 pandemic. A structured approach is essential for the management of this global crisis. The development of a reliable and effective treatment and fast vaccine deployment are crucial factors. Economic management is required, as well as special attention to patients with other underlying conditions like cancer, renal failure, diabetes and pregnant women [84]. Vaccines are our greatest hope, and transmission prevention should remain a priority to allow for the flattening of the epidemic curve and halt COVID-19 intensity. A better understanding of the disease spread, the initiation of vaccination drives, and adequately equipped healthcare facilities are cause of optimism, but slackness at the government or public levels may lay waste the gains obtained so far.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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